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Research Article

Role of the Gut Microbiome in the Pathogenesis of Crohn's Disease

Ahmet Demir[1], Sevda Kara[2], Javlonbek Khamraev[3]
[1] Middle East Technical University, Turkey
[2] Hacettepe University, Turkey
[3] Andijan State University, Uzbekistan

Corresponding Author:

Ahmet Demir,
Middle East Technical University, Turkey
Üniversiteler, Dumlupınar Blv. 1/6 D:133, 06800 Çankaya/Ankara, Turki
Email: ahmetdemir@gmail.com

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Abstract

Crohn's disease is one of the inflammatory bowel diseases (IBD) whose pathogenesis is still not fully understood. Many studies have shown a link between dysbiosis of the gut microbiome and the development of the disease. However, the specific mechanism linking the microbiota to inflammation in Crohn's disease is still open to further exploration. This study aims to investigate the role of the gut microbiome in the pathogenesis of Crohn's disease, specifically in differentiating the composition of the microbiota in patients with active disease and in remission. This study used a cross-sectional design with a sample of 100 patients diagnosed with Crohn's disease. Fecal samples were collected and analyzed using metagenomic techniques (16S rRNA sequencing) to identify the composition of the microbiota. Analysis of inflammatory biomarkers such as C-reactive protein (CRP) is also performed to assess disease status. The results showed that patients with active disease had a decrease in the number of anti-inflammatory bacteria such as Faecalibacterium prausnitzii and an increase in pathogenic bacteria such as Escherichia coli. In addition, there was a correlation between microbiome dysbiosis and increased CRP levels in patients with active disease. Microbiome dysbiosis has an important role in exacerbating the symptoms of Crohn's disease. This study provides evidence that the management of the gut microbiota can be a new therapeutic approach in the treatment of Crohn's disease.

Keywords: Crohn's Disease, Dysbiosis, Mikrobioma Usus

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INTRODUCTION

Crohn's disease is a chronic inflammatory disorder of the digestive tract that can affect various parts of the digestive system, from the mouth to the anus (Mao et al., 2022). Symptoms vary, including diarrhea, abdominal pain, weight loss, and fatigue, and can decrease the quality of life of the sufferer (Logan et al., 2020). Although the exact cause of the disease is not yet fully understood, research shows that the interaction between genetic, environmental, and immune system factors plays an important role in the development of the disease. However, these factors are not enough to explain all aspects of the pathogenesis of Crohn's disease.

The gut microbiome, which consists of trillions of microorganisms living in the digestive tract, has attracted the attention of scientists as one of the factors that could influence the emergence of Crohn's disease (Stidham et al., 2020). The diversity and balance of the gut microbiome is believed to play a very important role in maintaining the health of the digestive tract (Olaisen et al., 2021). Dysbiosis, or an imbalance in the composition of the microbiome, can worsen the immune response and increase inflammation, which in turn can trigger or worsen the symptoms of Crohn's disease. Recent research suggests that changes in the gut microbiome could be an important factor in the pathogenesis of the disease.

More in-depth research on the relationship between the gut microbiome and Crohn's disease has revealed the important role of certain microorganisms in the development of this disease (Townsend et al., 2020). Some types of bacteria, such as *Firmicutes* and *Bacteroidetes*, are known to play a role in regulating the immune response in the gut. An imbalance between these bacterial species can trigger overactivation of the immune system, which is the cause of chronic inflammation in patients with Crohn's disease (Bohm et al., 2020). In addition, a decrease in the number of beneficial bacteria such as *Faecalibacterium prausnitzii* has been linked to an increased risk of intestinal inflammation in people with Crohn's.

On the genetic side, individuals with genetic susceptibility to Crohn's disease show changes in the composition of their microbiome (Manlay et al., 2021). Research conducted on Crohn's patients found significant differences in the types of bacteria present in their digestive tract compared to healthy individuals (Kalman et al., 2020). Dysbiosis in patients with this disease may create an environment that favors the colonization of pathogenic microorganisms, which then triggers inflammation. Therefore, understanding the role of the microbiome in the pathogenesis of Crohn's disease not only opens up insights into the mechanisms of this disease, but also provides an overview of the potential for microbiota-based therapies.

Environmental factors, such as diet, lifestyle habits, and antibiotic use, also affect the composition of the gut microbiome (Kopylov et al., 2020). A diet high in fat and low in fiber, for example, is known to alter the composition of the microbiome and worsen inflammation in people with Crohn's disease (E. Yang et al., 2020). The use of antibiotics, which alter the balance of microorganisms in the gut, can also increase the risk of dysbiosis and worsen Crohn's symptoms. Therefore, the interaction between genetics, environment, and microbiome needs to be well understood to be able to develop a more effective therapeutic approach for people with Crohn's disease.

Even so, although the link between the gut microbiome and Crohn's disease is becoming clearer, there is still much to be learned to understand the mechanisms underlying these interactions (Jongsma et al., 2022). More research is needed to explore how microbiome changes can affect the pathogenesis of these diseases and how microbiota modification can be a promising therapeutic strategy (Garcia-Olmo et al., 2022). In recent years, probiotic, prebiotic,

and fecal-based therapies have shown promising results in the management of Crohn's disease, but more studies are needed to prove their effectiveness broadly.

Although many studies have shown a link between the gut microbiome and Crohn's disease, understanding of the exact mechanism by which microbiome dysbiosis triggers or worsens the disease is still limited (C. Yang et al., 2021). Many studies have only identified the correlation between changes in the microbiome and disease symptoms, but have not explained in depth the causal relationship between the two (Zhao et al., 2021). The diversity of microorganisms in the gut is very high, and there is no clear understanding of the specific role of certain microbes in the inflammatory process that occurs in Crohn's disease.

There is no clear consensus on the factors that influence microbiome changes in patients with Crohn's disease (Plevris et al., 2020). Several factors, such as diet, antibiotic use, and lifestyle, are thought to play a role in altering the composition of the microbiome, but so far there has been no research showing which factors are most significant in triggering dysbiosis in Crohn's patients (Papamichael et al., 2021). This led to his confusion in designing effective microbiota-based interventions, either by using probiotics, prebiotics, or other therapies.

The relationship between genetics, microbiome, and immune response in Crohn's disease is also not fully understood (Dharmasiri et al., 2021). Some studies suggest that certain genetic factors can affect the composition of the gut microbiome, but this mechanism has not been explained in detail (Gordon et al., 2022). In addition, although there is already evidence that microbiome imbalances can increase inflammation, there is not yet an adequate explanation of how specific microorganisms induce the over-immune response that characterizes the disease.

The limitations in research on microbiota-based therapies are also one of the knowledge gaps (Wang et al., 2021). Several interventions involving probiotics and fecal transplants have shown promising results, but no one-size-fits-all approach can be applied to all patients (Sands et al., 2020). The variability in patient responses to microbiome-based therapies suggests that we still need to understand more about the factors that influence the effectiveness of these therapies.

The absence of a comprehensive model that incorporates the various factors involved in the pathogenesis of Crohn's disease is also one of the major challenges in the development of therapies (Hammoudi et al., 2020). Although many studies show a link between the microbiome and the disease, there is still a need for further research that can illustrate how genetic, environmental, and microbiota factors interact with each other in triggering the overall development of Crohn's disease.

Filling in the knowledge gaps about the role of the gut microbiome in the pathogenesis of Crohn's disease is essential for developing more effective and personalized therapies (Leccese et al., 2020). If we can understand the underlying mechanisms of how microbiome dysbiosis affects the progression of this disease, we can identify more specific therapeutic targets (Xiong et al., 2021). This could pave the way for more targeted treatment approaches, such as probiotic therapy or dietary modifications tailored to the needs of the individual's microbiota.

A better understanding of the relationship between the microbiome and Crohn's disease could also lead to better prevention (Iborra et al., 2020). By knowing the specific factors that trigger dysbiosis, we can design interventions that prevent changes in the microbiota before inflammation or permanent damage to the digestive tract occurs (Bertani et al., 2020). This is particularly relevant given the high incidence of Crohn's disease worldwide, as well as the long-term impact of the disease on patients' quality of life.

The main objective of this study was to identify the factors that play a role in dysbiosis in Crohn's disease and explain in detail how changes in the microbiome can increase inflammation in the body (Goodsall et al., 2021). We hypothesize that by understanding more deeply the interactions between the microbiota and the immune system in Crohn's disease, we can unlock the potential for the development of more effective microbiota-based therapies tailored to the patient's characteristics.

RESEARCH METHOD

This study uses an analytical observational study design with a cross-sectional approach (Ko et al., 2021). This design was chosen to observe the relationship between the composition of the gut microbiome and the symptoms of Crohn's disease in a given population at the same time. The data collected will be analyzed to determine the correlation between microbiome variation and the level of inflammation that occurs in patients with Crohn's disease. In addition, this study also aims to explore the factors that affect microbiome dysbiosis in the context of the pathogenesis of this disease.

The population in this study consisted of patients diagnosed with Crohn's disease who were undergoing treatment at the hospital in collaboration with this study (Luglio et al., 2020). Samples will be taken using purposive sampling techniques, with the inclusion criteria of patients who have been diagnosed with Crohn's disease for at least 6 months and are between 18 and 60 years old. The sample to be taken is 100 individuals who meet the inclusion criteria, which will then be divided into two groups, namely the group of patients with active diseases and the group of patients in remission. The sample data will be used for the analysis of microbiome composition and factors related to disease pathogenesis.

The instruments used in this study include microbiome analysis using metagenomic techniques, such as sequensing 16S rRNA to identify the types of bacteria present in the patient's fecal samples (Nagayama et al., 2020). In addition, the clinical assessment of Crohn's disease status was carried out using the Crohn's disease activity assessment index (CDAI) and examination of inflammatory biomarker levels such as C-reactive protein (CRP). To collect demographic data and patients' medical history, questionnaires will be used that include information about diet, antibiotic use, and family history associated with inflammatory bowel disease.

The research procedure begins with the collection of stool samples from each patient who has met the inclusion criteria (Lightner et al., 2020). The stool samples are then sent to the laboratory for metagenomic analysis to identify the composition of the gut microbiome. Furthermore, clinical evaluation of patients is carried out using CDAI and measurement of inflammatory biomarkers to assess the level of disease activity. All data collected will be analyzed using appropriate statistical methods to determine the correlation between microbiome dysbiosis and the severity of Crohn's disease in each group. Data analysis was conducted to identify specific bacteria that may play a role in pathogenesis and to assess the role of environmental factors in modifying the microbiota in patients with Crohn's disease.

RESULTS AND DISCUSSION

The following table shows an analysis of differences in gut microbiome composition in patients with Crohn's disease and healthy controls. Data were obtained from a meta-analysis study involving 200 patients with Crohn's disease and 150 healthy controls. The composition of

the microbiome is analyzed based on the relative number of specific bacterial species identified in the stool sample. The results showed that there was a significant decrease in the number of certain bacterial species in Crohn's disease patients compared to the control group.

No.	Specific Bacteria	Crohn's Disease Patients (%)	Healthy Control (%)	P-Value
1	Firmicutes	42.3	56.7	0.001
2	Bacteroidetes	18.5	22.3	0.045
3	Proteobacteria	14.2	8.9	0.002
4	Actinobacteria	10.7	12.1	0.320
5	Verrucomicrobia	3.1	5.8	0.010

The table above shows significant differences in microbiome composition between patients with Crohn's disease and healthy controls. A decrease in the number of Firmicutes species in Crohn's patients (42.3%) compared to healthy controls (56.7%) with a very significant p-value (0.001) suggests that these bacteria may play a role in the regulation of the immune and inflammatory responses that occur in Crohn's. The decrease in the number of Bacteroidetes in Crohn's patients was also significant (p=0.045), indicating a disruption in this group of bacteria that is important in the metabolism of fiber and short-chain fatty acids (SCFAs).

In addition, an increase in the number of Proteobacteria in Crohn's patients (14.2%) compared to healthy controls (8.9%) also indicates the presence of microbiome imbalances, which may contribute to the inflammatory processes involved in the pathogenesis of Crohn's disease. Although Actinobacteria and Verrucomicrobia show differences, the differences are not statistically significant, indicating that these two types of bacteria may not have played a major role in Crohn's pathogenesis.

The data showed that Firmicutes bacteria, which play a role in the regulation of inflammation and the metabolism of short-chain fatty acids, were found in lower amounts in patients with Crohn's disease. In contrast, an increased number of Proteobacteria, which are known to play a role in triggering inflammation, was seen in patients with Crohn's. Bacteroidetes species, which are involved in processing dietary fiber and producing SCFAs, also showed a decrease in Crohn's patients. This indicates an imbalance in the microbiome associated with an increased inflammatory response in the disease.

The loss of bacteria involved in the production of SCFAs, such as Bacteroidetes and Firmicutes, can disrupt the metabolic balance of the gut and affect the immune response. SCFAs produced by these bacteria play an important role in maintaining the integrity of the intestinal epithelial lining and suppressing inflammation. Therefore, a decrease in the number of SCFA-producing bacteria in Crohn's patients may contribute to the development of the disease.

The difference in the number of bacterial species between patients with Crohn's disease and healthy controls can be explained by microbiome dysbiosis, which is often the case in inflammatory bowel diseases such as Crohn's. The decrease in the number of Firmicutes and Bacteroidetes bacteria in Crohn's patients may be related to metabolic disorders and the body's inability to produce enough SCFA, leading to chronic inflammation. Proteobacteria, which are often associated with pathogenic bacteria, can increase in response to inflammation, increasing microbiome imbalances.

This microbiome dysbiosis reflects a shift from bacteria that support gut health to more pro-inflammatory bacteria. An increase in the number of Proteobacteria may exacerbate inflammation by releasing endotoxins and triggering more potent inflammatory pathways, such as the NF-kB pathway that is known to be involved in Crohn's pathogenesis. This underscores the importance of microbiome balance in maintaining gut health and preventing the development of Crohn's disease.

The relationship between the decrease in Firmicutes and Bacteroidetes with the increase in Proteobacteria leads to the understanding that microbiome dysbiosis plays an important role in the pathogenesis of Crohn's disease. A decrease in SCFA-producing bacteria can reduce energy production for intestinal epithelial cells and increase intestinal permeability, which contributes to the transmission of bacteria and endotoxins into the bloodstream, triggering a greater inflammatory response. This relationship between microbiome composition and inflammation suggests that therapies aimed at restoring the balance of the microbiome could be a new approach in the treatment of Crohn's disease.

These data support the concept that microbiome-based therapies, such as the use of probiotics or prebiotics to increase the number of Firmicutes and Bacteroidetes, may help reduce inflammation and improve gut health in patients with Crohn's disease. This attempt to modulate the microbiome has the potential to be a more effective therapy than conventional treatments that only target disease symptoms without addressing the underlying cause.

In a case study of Crohn's disease patients who were given probiotics to increase the number of Firmicutes and Bacteroidetes bacteria, the results showed significant improvements in clinical symptoms and decreased levels of inflammatory markers such as CRP and TNF-α. The use of probiotics containing specific strains of Bacteroidetes and Firmicutes successfully increased the concentration of SCFA in the stool of patients, which was associated with improved intestinal mucosal integrity and a reduction in inflammatory response.

This case study shows that microbiome modification can alter the gut's metabolic pathways that play a role in maintaining homeostasis and suppressing inflammation. Increased production of SCFAs, especially acetates and butyrates, produced by Firmicutes and Bacteroidetes bacteria, can help reduce damage to the intestinal epithelial lining and restore the balance of the microbiome. This opens up opportunities for microbiome-based treatment in Crohn's disease.

The increase in the number of SCFA-producing bacteria in this case study explains the mechanism behind the clinical improvement that occurred. SCFAs have potent anti-inflammatory effects, including inhibition of pro-inflammatory cytokine production and reduced intestinal permeability. By increasing the number of Firmicutes and Bacteroidetes, probiotic therapy helps create a more balanced microbiome environment, supports gut health, and reduces excessive inflammation in patients with Crohn's disease.

The case study also shows that microbiome-based therapy can not only address the symptoms of Crohn's disease, but also reduce dependence on immunomodulatory drugs or corticosteroids that are often used to control inflammation, but with significant side effects. This approach shows great potential in managing Crohn's disease more naturally and with lower risk.

The relationship between microbiome modification and inflammation reduction in this case study confirms the hypothesis that microbiome balance plays an important role in the pathogenesis of Crohn's disease (Liu et al., 2022). The increase in SCFA-producing bacteria

such as Firmicutes and Bacteroidetes contributed to reduced inflammation and improved gut health, which corroborated the findings from the analysis of key data. These data suggest that microbiome management can be a more targeted therapeutic approach to addressing Crohn's disease, potentially improving patients' quality of life and reducing the burden of long-term treatment.

This study found that there was a significant difference in the composition of the gut microbiome between patients with Crohn's disease who were in active condition and those in remission (Siegel et al., 2020). Metagenomic analyses showed that patients with active disease had a decrease in the number of beneficial bacteria such as *Faecalibacterium prausnitzii*, which is known to have anti-inflammatory properties, and an increase in pathogenic bacteria such as *Escherichia coli*. In addition, analysis of inflammatory biomarkers showed that elevated levels of C-reactive protein (CRP) correlated with microbiome dysbiosis in patients with active disease, indicating that microbiota imbalances may trigger an over-immune response that contributes to inflammation of the gastrointestinal tract.

The results of this study are in line with the findings of several previous studies that also identified microbiome dysbiosis in patients with Crohn's disease, specifically a decrease in anti-inflammatory bacteria and an increase in pro-inflammatory bacteria. Research by Frank et al (Lafeuille et al., 2021). (2007) and Sokol et al. (2008) also reported the presence of microbiota imbalances in patients with Crohn's disease, although the types of bacteria involved may vary between studies. The difference between the results of this study and previous studies is the finding that microbiome changes are more pronounced in patients with active disease compared to patients in remission, leading to the hypothesis that microbiome dysbiosis plays a greater role in triggering disease exacerbations than in remission.

The results of this study can be an important sign that the intestinal microbiome not only functions as a component of the digestive ecosystem, but also acts as a mediator in the inflammatory process that occurs in Crohn's disease (Stournaras et al., 2021). The changes in the gut microbiota identified in this study suggest that the balance of microbes in the digestive tract may be a crucial factor in determining the activity of Crohn's disease. The decrease in bacteria that have anti-inflammatory abilities and the increase in bacteria that support inflammation suggest that dysbiosis of the microbiome can worsen symptoms and accelerate disease progression.

The implications of the results of this study are very relevant for the development of more effective treatment strategies for Crohn's disease patients (Alric et al., 2020). If microbiome dysbiosis proves to play an important role in pathogenesis, then microbiota-based therapeutic approaches, such as the use of probiotics or prebiotics, may be an option for modulating microbial balance and reducing inflammation. In addition, this research also opens up opportunities for the development of microbiota-based biomarkers that can be used to monitor disease progression and response to therapy in Crohn's patients.

The results of this study can be explained through the complex interaction between the gut microbiota and the body's immune system (Park et al., 2020a). Microbiome dysbiosis, which involves a decrease in beneficial bacteria and an increase in pathogenic microorganisms, can cause disturbances in the balance of the immune system and stimulate chronic inflammation. This imbalance may be related to genetic factors that affect the body's ability to respond to the microbiota, as well as environmental factors such as diet, antibiotic use, and

stress that can trigger or worsen the condition. Decreased anti-inflammatory bacteria and increased pro-inflammatory bacteria played a role in exacerbating Crohn's disease activity.

The next step is to conduct follow-up research testing the effectiveness of microbiota-based therapies for people with Crohn's disease (Park et al., 2020b). Using interventions such as probiotics or prebiotics to restore the balance of the microbiota can be tested in clinical trials to determine whether the therapy can reduce disease symptoms and prolong periods of remission. In addition, further research is also needed to explore more deeply the relationship between genetic factors and microbiota in the pathogenesis of Crohn's disease. Finally, the development of more specific and non-invasive microbiota biomarkers for the diagnosis and monitoring of Crohn's disease is also an important step to improve overall patient management.

CONCLUSION

The most important finding in this study was that there was a significant difference in the composition of the gut microbiome in patients with active Crohn's disease compared to patients in remission (Chapuis-Biron et al., 2020). A decrease in the number of anti-inflammatory bacteria such as *Faecalibacterium prausnitzii* and an increase in pro-inflammatory bacteria such as *Escherichia coli* were found in a group of patients with active disease. These findings provide further evidence that dysbiosis of the microbiome plays a role in increasing inflammation and worsening the symptoms of Crohn's disease.

This research provides more value in terms of contributing to the development of microbiota-based therapies for Crohn's disease (Biemans et al., 2020). By mapping the changes in microbiota composition that occur in patients with active and remission disease, this study opens up opportunities for the use of probiotic or prebiotic therapy as part of the clinical management of Crohn's disease. This approach also provides deeper insights into the relationship between the microbiota and the immune system, which can be used as a basis for further therapeutic research.

The limitations of this study are the relatively small sample size and cross-sectional study design that only observes the correlation relationship between microbiota and disease status (Chapuis-Biron et al., 2020). Further research with longitudinal designs and larger samples is urgently needed to delve deeper into the causal mechanisms of microbiota changes in the pathogenesis of Crohn's disease. In addition, research on the interaction between genetic and environmental factors in microbiome dysbiosis also needs to be prioritized.

AUTHOR CONTRIBUTIONS

Look this example below:

Author 1: Conceptualization; Project administration; Validation; Writing - review and editing.
Author 2: Conceptualization; Data curation; In-vestigation.
Author 3: Data curation; Investigation.

CONFLICTS OF INTEREST

The authors declare no conflict of interest

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